REMARKS

Rejections Under 35 U.S.C. § 103

The Examiner has rejected the instant Application under 35 U.S.C. §103(a) stating one of skill in the art would have been motivated to combine the teachings of Ray, McCluskie and Paoletti to produce the instant invention. According to the Examiner, Ray et al. teach a method of inducing a protective serum neutralizing antibody response against rabies in mice by administering a plasmid encoding rabies glycoprotein G, while McCluskie et al. teach complexing plasmid DNA with a cationic lipid, specifically tetramethyltetraalklyl spermine analog lipid within the range of the instant DNA:lipid ratio claimed, and the use of such a complex to generate antibodies in mice. The Examiner further states Paoletti teaches the use of recombinant poxviruses to induce a protective immune response against rabies in a cat.

It is well-established that a showing of obviousness requires a teaching, suggestion or motivation to combine or modify prior art references coupled with a reasonable expectation of success. *Boehringer Ingelheim Vetmedica Inc. v. Schering-Plough Corp*, 65 USPQ2d 1961 (Fed. Cir. 2003). The Examiner contends that in view of Paoletti, one of skill in the art at the time the invention was made would have been motivated to use the plasmid-cation lipid construct of Ray et al. and McCLuskie et al. to vaccinate cats against rabies. Applicants respectfully disagree with the Examiner's conclusory statement and submit that not only is the combination of Paoletti with Ray and McCluskie improper, but that even if such a combination was proper, the references and the state of the art at the time of filing would not have led to a reasonable expectation of successfully vaccinating cats against rabies using plasmid-cationic lipid complexes.

To begin with, Applicants assert the prior art references fail to provide any teaching or suggestion that would motivate one skilled in the art to combine Paoletti with either Ray et al. or McCluskie et al. Applicants note both Ray et al. and McCLuskie et al. teach using naked DNA or DNA/lipid complexes whereas Paoletti teaches using a recombinant virus. Applicants contend the use of naked or complexed DNA to induce a protective immune response cannot be equated with the use of a recombinant virus to induce such a response. Viruses are natural organisms that, due to evolutionary pressure, have evolved well-developed systems for entering the cells of host organisms and usurping the cellular machinery for the expression of viral genes.

Viruses contain molecules, such as receptor proteins, that aid in attachment, entry and expression of the viral nucleic acid molecule(s). Millions of years of evolution have ensured that if a virus is introduced to a host cell, the virus will enter the cell, viral gene expression will ensue and the virus will be amplified and spread to neighboring cells. In contrast, DNA vaccines are synthetic constructs lacking the evolutionarily-selected machinery to assist in the attachment, entry or expression of the nucleic acid component. Not having been subject to the same selective pressure as have viruses, the ability of DNA vaccines to enter a host cell and enable gene expression within that cell is much less predictable. Furthermore, DNA vaccines do not have the intrinsic ability to amplify and spread within the vaccinated animal. For these reasons, Applicants contend the intrinsic abilities and mechanisms involved in entering a host and inducing an immune response are inherently different between viruses and DNA vaccines and, therefore, these two methods of vaccination are not obviously interchangeable or even comparable. Most importantly, Applicants note neither Ray et al. nor McCluskie et al. teach or suggest that naked or complexed DNA is equivalent to a virus in the generation of an immune response. Likewise, Paoletti does not teach or suggest that a DNA vaccine could be used instead of a virus. Therefore, Applicants submit there is no teaching or suggestion in any of the cited references that would motivate one skilled in the art to substitute DNA:lipid constructs in place of a recombinant virus in the cat vaccination system of Paoletti.

In addition, Applicants note the authors in McCluskie et al. themselves cautioned against extrapolating results between species due to physical and physiological differences between different animals (page 411, right-hand column, bottom paragraph through page 412, left-hand column, top paragraph). As a result, Applicants submit McCluskie et al. do not provide any motivation to combine their teaching with those of Paoletti to immunize cats using a plasmid-cationic lipid complex. In fact, in view of McCluskie's statements that the results in mice may not be predictive for other animals, contrary to the Examiner's contention Applicants contend McCluskie et al. actually teach away from the combination of references suggested by the Examiner.

Next, assuming the references are properly combinable, which Applicants strongly disagree, Applicants assert the state of the art at the time of filing did not allow one skilled in the art to have a reasonable expectation of successfully vaccinating cats using DNA:lipid complexes. Applicants note the instant invention is specifically drawn to vaccinating cats, whereas the work

of Ray et al. and McCluskie et al. was performed in mice. In attempting to bridge this gap, the Examiner has cited the work of Paoletti, which teaches virally-based vaccination of cats against rabies, stating this teaching would lead one skilled in the art to have a reasonable expectation of successfully immunizing cats using a plasmid-cation lipid complex. Applicants assert that, contrary to the Examiner's assertion one skilled in the art would not have had a reasonable expectation of successfully immunizing cats using a plasmid-cation lipid complex. This assertion is based on two key points: (1) the state of the art at the time of filing and (2) the evidence available at the time of filing with regard to cross-specie extrapolation of vaccination results.

With regard to the state of the art, Applicants note that at the time the invention was made, the effect on vaccination efficacy of various factors, such as the type of lipid used, the route of administration or the specie of animal being vaccinated, was unclear. In fact, Applicants contend the state of the DNA vaccine art at the time was one of general confusion with regard to these factors and their effects on vaccination efficacy. In support, Applicants direct the Examiner's attention to the specification, for example, page 2, lines 8-31 through page 4, lines 1-4 and page 4, lines 27-31 through page 5, lines 1-6, where this environment of general confusion is discussed and several examples highlighting this confusion are given. These sections of the specification clearly illustrate, for example, that while a DNA vaccine may work by one route of administration or in one specie of animal, the same DNA vaccine would fail to work when administered by another route or when given to a different specie of animal. Additionally, the specification notes there is little understanding of the basis for such discrepancies.

More significantly, Applicants submit that direct evidence available at the time of filing suggests it was not possible to extrapolate vaccination results from one species to another. Therefore, one skilled in the art would be unable to predict whether a DNA vaccination method that worked in one specie would work in a different specie. As noted above, the authors in McCluskie et al. themselves cautioned against extrapolating results between species due to physical and physiological differences between different animals. While in that case, McCluskie et al. were referring to extrapolation of results from mice to humans, Applicants contend the general idea that studies in mice may not be indicative of what would happen in other animals is applicable in the instant application. In fact, experimental evidence available at the time suggested that a DNA vaccine would behave differently in mice and cats. For example, the

specification at page 3, lines 28-30 through page 4, lines1-4, states that, based on work performed by two of the inventors, DNA vaccination efficacy in cats is inferior to that seen in mice given the same plasmid construct; (see also *Vaccine*, March 5, (1999) 1109-1116, a copy of which is attached). Furthermore, Example 9 in the specification demonstrates that cationic lipid formulation of a DNA vaccine failed to enhance vaccine efficacy in mice although the same formulation does enhance vaccine efficacy in cats; (see page 31, lines 25-28, of the specification). As noted by the court in *Boehringer Ingelheim Vetmedica Inc. v. Schering-Plough Corp*, 65 USPQ2d 1961 (CAFC 2003), "...there can be little better evidence negating an expectation of success than actual reports of failure." Clearly, the evidence cited above demonstrates the failure of the predictive value of mice with regards to vaccinating cats. In view of the cumulative evidence discussed above, Applicants assert mice have no predictive value with regard to the efficacy of a vaccine in cats. Therefore, since the DNA:lipid work of Ray et al. and McCluskie et al. was performed in mice, one skilled in the art would not have been motivated to use the DNA:lipid complexes of to immunize cats with any reasonable degree of success.

CONCLUSION

In view of the above arguments, Applicants request the obviousness rejection be withdrawn and solicit an allowance of the instant claims.

If there are any questions, the Examiner is encouraged to contact the undersigned.

Respectfully submitted,

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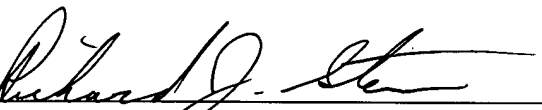
By: 

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